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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,654	01/29/2001	Tsvee Lapidot	LAPIDO2	2645

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,654	LAPIDOT ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *123-126 and 128-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *123-126, and 128-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response received on 5/16/05 has been entered. Claims 1-122, and 127 are canceled. Claims 123-126, and 128-131 are currently pending and under examination. An action on the merits follows.

Those sections of Title 35, not included in this office action can be found in the previous office action.

Claim Rejections - 35 USC 103

The rejection of claims 123-126, and 128-131 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,541,103, 7/30/96, hereafter referred to as Kanz et al. in view of Mohle et al. (1998), Blood, Vol. 91, No. 12, 4523-4530, is maintained.

Applicant's amendments to the claims and arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the Declaration under 37 CFR 1.132 by Dr. Lapidot establishes that the applicant's methods yield unexpected results over the methods taught by the prior art and further establishes why following the teachings of Kanz et al. and Mohle et al. would not lead the skilled artisan to the present invention. As such, the applicant argues that the claimed invention is patentable.

The declaration by Dr. Lapidot, one of the applicants in this application, discusses the results of examples 3 and 4 present in the specification as filed. Dr. Lapidot states that two populations of stem cells were treated for a short period of time, 40 hours, with SCF. The first population of cells were CD34+ cells from adult mobilized peripheral blood (PBL) which applicant states has only a small percentage of CD38- cells , and the second population comprised a sorted population of CD34+/CD38-/low/CXCR4-/low cells derived from cord blood. According to the applicant, 40 hours of stimulation of either cell population with SCF alone did not result in cell expansion but did result in increased expression of CXCR4. The applicant further states that the resulting cell population with increased CXCR4 expression derived from either the peripheral blood CD34+ population stimulated with SCF or the cord blood CD34+/CD38-/low population stimulated with SCF and further selected for migration in response to SDF showed increased engraftment compared to the cell populations not treated with SCF for 40 hours. The applicant also states the these cells showed enhanced self renewal capacity *in vivo* following transplantation.

Dr. Lapidot then compares these results with the teachings of Kanz and Mohle. According to Dr. Lapidot, Kanz et al. was concerned with expanding the number of CD34+ stem cells and teaches that expansion occurs following the culture of the cells with a combination of cytokines and growth factors including IL6 and SCF. The applicant states that Kanz is silent regarding the expression of CXCR4 before or after exposure to the cytokines and growth factors or the self-renewal potential of the cells so treated *in* vivo. The applicant further states that expansion was not seen when the cells were treated with SCF or SCF and IL-6 alone. Thus, the applicant states that Kanz et al. teaches away from using SCF and IL-6 alone. Regarding Mohle,

the applicant argues that Mohle does demonstrate that the CD34+ CXCR4+ cell population purified using the sorting method of Mohle, i.e. sorting by migration in response to SDF, are actually stem cells since their work was done *in vitro*, and further that nothing in Mohle suggests that the cells obtained using the SDF sorting method would be capable of self-renewal *in vivo*. Thus, the applicant concludes that since the Kanz et al. "teaches away" from treating CD34+ with SCF or SCF and IL-6 alone and that neither Kanz nor Mohle teach or suggest that a cell population stimulated with SCF alone and sorted by migration to SDF would have the "unexpected" self renewal capacity observed by applicants.

In response, the MPEP in section 716.02(d) states that in the consideration of evidence of unexpected results, "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the 'objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support.'", citing *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) (see also *In re Peterson*, 315 F. 3e 1325, 1329-31, 65 USPQ2d 1379, 1382-85 (Fed. Cir. 2003), and *In re Grasselli* 713 F.2d 731, 741, 218 USPQ 769, 777 (Fed. Cir. 1983)). In the instant case, the evidence provided to demonstrate "unexpected results" and thus non-obviousness is not commensurate in scope with the claims as written. The claims as written are directed to methods for preparing a cell composition consisting essentially of human hematopoietic CD38-/low CXCR4+ stem cells capable of migrating in response to SDF and methods for increasing a population of hematopoietic CXCR4+ stem cells. Both methods broadly recite two method steps, the first comprising stimulating a population of CXCR4-/low or CD38-/low CXCR4-/low stem cells for up to five days with a suitable agent selected from a group consisting of a lectin, a cytokine, a

type of mammalian stromal cell or mixtures therefore, and a second step comprising sorting out CXCR4+ or CD38-/low CXCR4+ stem cells that migrate in response to SDF. The applicant's arguments concerning the "unexpected" property of self-renewal is directed to CD34+ CXCR4+ or CD34+ CD38-/low CXCR4+ stem cells produced by stimulating CD34+ cells or CD34+/CD38-/low/CXCR4-/low cells for 40 hours with SCF alone followed by the sorting of CD34+ CD38-/low CXCR4+ stem cells that migrate in response to SDF. However, applicant's claims are not so limited and broadly read on stimulating CXCR4-/low or CD38-/low CXCR4-/low stem cells with any one or more agents from the genuses of lectins, cytokines, and stromal cells. It is unclear from the evidence provided that stimulating a population of CXCR4-/low CD38+ or CXCR4-/low CD34- stem cells with any lectin, stromal cell, or cytokine other than SCF for a period of 40 hours would in fact generate a population of cells with the self-renewal capacity observed by applicants. Thus, the evidence of an "unexpected property" is clearly not commensurate in scope with the claims as written.

Further, regarding the applicant's citation of three post-filing publications in support of "unexpected results" using other suitable "agents", the three publications cited, Schioppa et al., Danet et al., and Ceradini et al., were all published years after the effective filing date of the instant application and teach the use of low O2 levels to increase CXCR4 expression. However, it is noted that the claims as written do not encompass the use of hypoxia to increase CXCR4 expression, and further the specification as filed does not teach or suggest that hypoxia could increase CXCR4 expression. Thus, the post-filing evidence presented in the declaration is not relevant to the claims as written.

In addition, while the applicant's claims recite stimulating for up to five days, a range of time including 1 hour or less to 120 hours, the applicant's results were obtained using a single time of stimulation, i.e. 40 hours. To establish unexpected results over a claimed range, applicants should compare a sufficient number of tests both inside and outside the claimed range to show the criticality of the claimed range. *In re Hill*, 284 F.2d 955, 128 USPQ 197 (CCPA 1960). The applicant has not met this standard to demonstrate that stimulation with SCF or any of the other claimed lectins, cytokines, or stromal cells, for any time other than 40 hours would result in a cell population with the properties discussed by the Lapidot declaration.

Furthermore, as discussed in previous office actions, Kanz et al. teaches the preparation of hematopoietic stem cells useful for transplantation comprising stimulating cells with mixtures of cytokines including SCF-1 and IL-6 (Kanz et al., columns 1 and 7-8). In particular, Kanz et al. teaches that CD34+ cells derived from peripheral blood treated with SCF-1 and IL-6 expand in culture and demonstrate increased colony forming potential which increases their usefulness for transplantation (Kanz et al., columns 3-4). It is further noted that Kanz et al. teaches the stimulation of the cells with the growth factor for "up to 28 days" (Kanz et al, column 6, line 25), a range that includes 5 days or less. As noted in the previous office action, the range recited in the claims lies within the range taught by Kanz et al., and that the MPEP states, " In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990)" MPEP 2144.05.

While the office agrees that Kanz et al. does not specifically teach that the administration of SCF-1 and IL-6 results in increased expression of CXCR4 on these, Kanz et al. does teach the

exact method steps recited by the claims for up-regulating surface CXCR4 expression. The MPEP states that, AWhere the claimed and prior art products are identical or substantially identical in structure or compositions, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. MPEP 211.01 and *In re Best*, 195 USPQ 430, 433 (CCPA 1997). Further, applicant's argument that Kanz teaches away from stimulating with only SCF alone or IL-6 alone could only apply at best to claims 129 and 131. The remaining pending claims read broadly on using combinations of cytokines such as taught by Kanz et al. However, it is not agreed that Kanz teaches away from stimulating with SCF alone. It is also noted that while Kanz et al. teaches that stimulation with the mixture of cytokines is preferred, Kanz et al. does not teach that CD34+ stem cells treated with SCF alone or SCF and IL-6 are not useful in transplantation. Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994).

In regards to the teachings of Mohle et al., applicant's argument that the cells produced by the sorting method of Mohle were not demonstrated to be "stem cells" by *in vivo* transplantation, Mohle et al. clearly teaches that the cell populations used prior to sorting comprised primitive CD34+ CD38- cells which are art recognized as being "stem cells". Further, Kanz et al. clearly demonstrates that CD34+ hematopoietic cells derived from peripheral blood do in fact contain stem cells capable of repopulating the blood following *in vivo* transplantation.

Further, contrary to applicant's argument that the skilled artisan wouldn't have been motivated to use the sorting method taught by Mohle with the methods of Kanz et al., Mohle et al. clearly teaches that CD34+ CXCR4+ hematopoietic progenitor cells which migrate in response to SDF-1 would have enhanced capability to migrate and home to the bone marrow which would increase their usefulness for transplantation (Mohle et al., pages 4523 and 4528). Thus, based on the teachings provided by Mohle et al. for sorting primitive CXCR4+ CD34+ $CD38^{-/low}$ hematopoietic progenitor cells which transmigrate in response to SDF-1 for use in transplantation in order to increase stem cell homing and migration, the skilled artisan would have been motivated to further purify the CD34+ stem cells stimulated with SCF alone or other cytokines as taught by Kanz et al. by using the transmigration assay taught by Mohle et al.

Claim Rejections - 35 USC 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 123-124 and 128-129 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicant's amendments to claim 123.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER